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Review

Contemporary Use of β-Blockers: Clinical Relevance of Subclassification

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ABSTRACT

β-Adrenergic receptor blockers or β-blockers represent one of the oldest classes of cardiovascular agents and have been considered a cornerstone therapy for hypertension and heart disease for the past 5 decades. They are advocated as a first-line treatment for uncomplicated essential hypertension in patients younger than 60 years of age as recommended by the Canadian Hypertension Education Program. However, despite the well-established antihypertensive and cardiovascular benefits of β-blockers, a number of studies argue that they might not have the same clinical advantages of other classes of agents in terms of morbidity/mortality outcomes. This review will focus on the heterogeneity of the pharmacologic characteristics of β-blockers, and we will discuss the metabolic and hemodynamic differences within the β-blocker class and try to assess the potential implications of these differences for optimal selection in hypertension.

RÉSUMÉ

Les bloqueurs des récepteurs β-adrénergiques ou β-bloqueurs représentent l'une des plus anciennes classes d'agents cardiovasculaires et ont été considérés comme étant la pierre angulaire du traitement de l'hypertension et de la cardiopathie au cours des 5 dernières décennies. Ils sont recommandés par le Programme éducatif canadien sur l'hypertension comme traitement de première intention de l'hypertension essentielle non compliquée chez les patients de moins de 60 ans. Cependant, en dépit des avantages bien établis des β-bloqueurs contre l'hypertension et les maladies cardiovasculaires, de nombreuses études soutiennent qu'ils pourraient ne pas avoir les mêmes avantages cliniques que les autres classes d'agents en matière de résultats sur la morbidité et la mortalité. Cette revue mettra l'accent sur l'hétérogénéité des caractéristiques pharmacologiques des β-bloqueurs. De plus, nous discuterons des différences métaboliques et hémodynamiques au sein de la classe des β-bloqueurs, et essaierons d'évaluer les implications potentielles de ces différences pour réaliser une sélection optimale lors d'hypertension.

β-blockers represent one of the oldest classes of cardiovascular agents and have been considered a cornerstone therapy in heart disease such as heart failure[1] and acute myocardial infarction (MI).[2] They are indicated for uncomplicated essential hypertension in patients younger than 60 years of age.[3] Despite the well established antihypertensive benefits of β-blockers, some argue that they might not have the same clinical advantages of other classes of agents in terms of morbidity/mortality outcomes in patients with hypertension.[4,5] β-blockers represent a heterogeneous group of agents possessing several pharmacological properties that differentiate them and this might have a significant effect on clinical end points. In addition, these properties might influence their tolerability and adherence profile that frequently limit their use in clinical practice.[6-9] For the clinician and for the patient, adherence is quite important because adherence is a key element in chronic disorders such as hypertension and coronary artery disease (CAD).[10] The role of β-blockers in hypertension has been challenged by recent meta-analyses that found that stroke reduction might not be optimal when compared with other classes of antihypertensive agents.[4,5,11] In this article, the efficacy of β-blockers will be discussed, with a focus on the different pharmacologic characteristics. In addition, as discussed in a previous article,[12] the authors will discuss the potential clinical implications of these differences important for the clinician prescribing them.

Mechanism of Action

β-blockers reduce sympathetic nervous system activity through blockade of adrenergic receptor subtypes, particularly β1, β2, and β3. β1 receptors are primarily in the heart and some of the beneficial effects of blockade include bradycardia and improved diastolic coronary filling time, reduced oxygen requirements, and a reduction of renin, all beneficial in heart failure and myocardial ischemia. β2 receptors are mostly

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located in smooth muscle of blood vessels and the bronchial tree and stimulation leads to dilation. β3 receptors are located in adipocytes and the heart, and blockade by nonselective agents might contribute to their weight-increase and metabolic effects.[13] β-blocker specificity refers to the drugs' greater affinity for β1 receptors over β2 at usual drug levels, and therefore specificity for cardiac effects, and nonspecific agents that also block β2 receptors reduce antihypertensive activity.[14] Since the work of Raymond Ahlquist[15] and James Black,[16] many different β-blockers with distinct pharmacologic and hemodynamic properties were developed (Table 1). A total of 12 orally administered β-blockers are currently available in Canada. The second-generation β-blockers (atenolol, bisoprolol, etc) were developed with a higher affinity for the β1 receptor and are called cardioselective β-blockers. Blood pressure (BP) reduction for these more traditional first- and second-generation β-blockers might be achieved through a reduction in cardiac output, through heart rate and contractility reduction, but no beneficial effect or even an increase in peripheral vascular resistance.[20] The third generation β-blockers (carvedilol, labetalol, nebivolol) have vasodilating properties mediated by α-adrenoreceptor blockade and/or through nitric oxide (NO) release.[21] They reduce BP by decreasing peripheral vascular resistance while maintaining or increasing cardiac output.[21] Finally, β-blockers also differ in other pharmacologic characteristics such as lipophilicity and intrinsic sympathetic activity (ISA).

Efficacy of β-Blockers as a Monolithic Class

Hypertension

There is a misconception that this class of agents might not lower BP equivalently to other classes of antihypertensive agents. A meta-analysis published by the Blood Pressure Treatment Trialists' Collaboration[22] involving 37,872 patients and comparing different classes of antihypertensive agents (angiotensin-converting enzyme inhibitors, calcium channel blockers, β-blockers and/or diuretics) has shown that differences in outcomes were minimal on a 2- to 8-year follow-up duration for the same BP-lowering. Some have also questioned the efficacy of β-blockers in terms of hard end points, especially on stroke prevention, when compared with other classes of antihypertensive agents (see Khan et al., in this issue of the *Canadian Journal of Cardiology*[23]). Khan and McAlister published a meta-analysis in 2006 on 145,811 patients from 21 hypertension trials.[24] Their results showed that, in placebo-controlled trials and active comparator studies, β-blockers reduced major cardiovascular outcomes in younger patients but not in older patients, with the excess risk being particularly marked for stroke. It has been shown that the nonvasodilating β-blockers, such as atenolol, lower BP by reducing cardiac output while systemic vascular resistance remains unchanged or actually increases, simulating the effect of aging.[25] In elderly individuals, low cardiac output and increased peripheral resistance due to noncompliant arteries typically characterize their hemodynamic profile.[26] In younger patients, particularly linked to obesity and the metabolic syndrome, greater sympathetic activity leads to an increase in cardiac output and heart rate and increased peripheral vascular resistance, in part due to endothelial dysfunction. In this setting, a β-blocker with vasodilating properties might lead to a correction of these pathological changes.[25] Consequently, in light of these data, the Canadian Hypertension Education Program still recommends that β-blockers be used as the initial therapy for hypertension in uncomplicated patients younger than 60 years of age.[3]

Angina and MI

β-blockers remain the standard of care for patients with CAD, particularly for those having experienced an acute MI.[27] Benefits of β-blockers on cardiovascular outcomes seem to be in direct relation to β1-receptor blockade and not on the selectivity because atenolol and metoprolol have shown similar results on mortality in patients who have had an MI.[17] Indeed, β-blockers decrease the work of the heart by reducing heart rate, contractility, and systolic BP. For example, a chart review study of more than 69,000 patients treated with β-blockers after an MI has demonstrated that β-blockers were associated with a 40% improvement in survival and that β-blocker subtype had little influence on mortality[28]; the different subtypes of β-blockers all demonstrated significant reductions in mortality.[29,30] However, β-blockers with ISA have been associated with reduced clinical benefits in patients who have had a recent MI.[31] The role of β-blockers in patients with coronary risk

Table 1. Pharmacological properties of the different β-blockers

Drug	β1-Blockade potency ratio	β1/β2 selectivity	ISA	Lipophilicity	Half-life (hours)	Other
Nadolol	1.0	0	0	Low	12-24	
Pindolol	6.0	0	++	High	3-4	
Propranolol	1.0	0	0	High	3-4	
Sotalol	0.3	0	0	Low	12	Antiarrythmic effects
Timolol	0.6	0	0	High	4-5	
Acebutolol	0.3	+	+	Moderate	3-4	
Atenolol	1.0	+	0	Low	6-9	
Bisoprolol	10.0	++	0	Moderate	9-12	
Metoprolol	1.0	++	0	High	3-4	
Labetolol	0.3	+	0	Low	3-4	α_1-Blocking effect, direct β-vasodilation
Carvedilol	10.0	0	0	Moderate	7-10	α_1-Blocking effect
Nebivolol	10.0	+++	0	Moderate	8-27	Endothelium-dependent, NO-mediated vasodilation

0, absent; +, low; ++, moderate; +++, strong; ISA, intrinsic sympathetic activity; NO, nitric oxide.
Adapted from Manrique et al.,[17] Frishman and Saunders,[18] and Mason et al.[19]

factors or a remote MI or stroke was assessed in a recent meta-analysis, regrouping 44,708 patients from the **Re**duction of **A**therothrombosis for **C**ontinued **H**ealth (REACH) Registry, demonstrated that β-blockers were not associated with a lower risk of the composite cardiovascular event after a 44-month median follow-up.[27] However, in patients with an MI within 1 year of enrollment to the study, the use of β-blockers was associated with an improvement of the secondary outcome (cardiovascular death, nonfatal MI, nonfatal stroke, and hospitalization for atherothrombotic events).[27]

Heart failure

Patients with heart failure in whom there is no contraindication should receive a β-blocker on a background of angiotensin-converting enzyme-inhibition. These agents act by decreasing sympathetic nervous system activation and thereby improve morbidity and mortality outcomes. In this regard, results from major studies involving bisoprolol,[32] carvedilol,[33] and metoprolol[34] have demonstrated significant morbidity and mortality benefits, with a mortality reduction of approximately 35% across trials.[35] In Canada, only these 3 β-blockers possess the indication in heart failure. In heart failure, the degree of ISA impairs efficacy with bisoprolol, carvedilol and metoprolol having no ISA. When carvedilol was compared with metoprolol in patients with chonic heart failure in the **C**arvedilol **O**r **M**etoprolol **E**uropean **T**rial (COMET), carvedilol was found to be superior.[36] Similarly, carvedilol was found to reduce hospitalization for heart failure or death in the **M**ulticenter **A**utomatic **D**efibrillator **I**mplantation **T**rial with **C**ardiac **R**esynchronization **T**herapy (MADIT-CRT) study.[37] Interestingly, in the **B**eta-blocker **E**valuation of **S**urvival **T**rial (BEST) trial, bucindolol, a nonselective β-blocker with weak α-blocking properties, also reduced hospitalization for heart failure.[38] However, all-cause mortality was significantly reduced by 23%, but only in patients who had a systolic BP > 120 mm Hg.[38] The **S**tudy of the **E**ffects of **N**ebivolol **I**ntervention on **O**utcomes and **R**ehospitalisation in **S**eniors with Heart Failure (SENIORS) in 2128 patients aged 70 years and older with heart failure independent of left ventricular ejection fraction at entry demonstrated that nebivolol significantly reduced the composite outcome of all-cause mortality and cardiovascular hospital admission by 14% but not the risk of all-cause mortality compared with placebo.[39] However, in a subgroup of patients with low left ventricular ejection fraction (< 35%) and a median age of 75 years, mortality was reduced by 38%, showing similar results as those reported with other agents. Cruickshank suggests that the ISA on the β2 and the β3 receptors is responsible for the reduction of effect on heart failure with nebivolol.[40] However, this is not supported by the work of Brixius et al., showing that nebivolol seems devoid of ISA in human myocardium.[41]

Pharmacological Differences and Their Clinical Implications

Cardioselectivity

By definition, β1/β2-selectivity, or cardioselectivity, represents the pharmacological characteristic of an agent that will preferentially block β1 receptors, predominantly present in the heart and renal juxtaglomerular apparatus, and consequently have less influence on vascular smooth muscle and bronchial β2 receptors. This feature possessed by many β-blockers is of interest in clinical practice but the extent of selectivity is not absolute and ranges widely among the agents.[42] Bisoprolol and nebivolol have the highest β1 selectivity profile compared with other β-blocking agents commonly used.[17] Of note, this clinical feature is influenced by the magnitude of the dose and even cardioselective agents can exert some inhibition of β2-receptors, at higher dosage (equivalent to > 50 mg/d metoprolol).[18]

In terms of BP reduction, it seems that cardioselectivity might influence the extent of the antihypertensive effect. In fact, nonselective agents, by their blocking effect on β-2 vasodilatory receptors, might be less effective than cardioselective agents, those agents demonstrating less systolic BP variability compared with nonselective agents.[14] Bisoprolol 10 to 20 mg once daily has indeed been shown to lower BP more effectively than atenolol 50 to 100 mg once daily, a moderately cardioselective β-blocker.[43] The **A**nglo-**S**candinavian **C**ardiac **O**utcomes **T**rial (ASCOT)[44] examined 19,257 hypertensive patients with at least 3 other risk factors and treated with either an amlodipine-based treatment or an atenolol-based treatment. Results favoured the amlodipine-based treatment over atenolol for BP-lowering, metabolic effects, and hard outcomes. A substudy of the ASCOT trial, the **C**onduit **A**rtery **F**unction **E**valuation (CAFE) trial,[45] investigated the effects of both study treatments on brachial and central aortic pressures, finding that the amlodipine-based therapy decreased central systolic pressure significantly more than the atenolol-based treatment, possibly contributing to more strokes in the atenolol-based treatment group. A recent Cochrane review concluded that, based on the literature comparing β-blockers, especially atenolol, with placebo and other classes of agents, the evidence does not support their use as first-line drugs in the treatment of hypertension.[46] Cardioselectivity was not found to reduce aortic pulse pressure in a recent study comparing bisoprolol with atenolol.[47]

Bronchial reactivity in asthma appears to be less enhanced with more cardioselective β-blockers and is a concern with nonselective agents.[48] A meta-analysis demonstrated less adverse respiratory effects in patients with "mild-to-moderate reactive airway disease",[49] but reactive airways disease still remains a limitation for the use of these agents in clinical practice.

Vasodilation

In addition to their β1 receptor-blocking activity, third generation β-blockers also exert their clinical effects through vasodilatory properties. In Canada, labetalol and nebivolol are indicated for the treatment of hypertension and carvedilol is indicated for the treatment of heart failure. On a mechanistic point of view, carvedilol and labetalol are vasodilatory through α1-adrenoreceptor antagonism. Carvedilol has also been associated with an increase in plasma levels of NO that occurs through stimulation of NO synthase.[50] Nebivolol has vasodilatory properties through increased NO bioavailability, which seems mainly responsible for its clinical effect.[21] Others have also suggested activation of β3 adrenoreceptors as a

possible mechanism explaining the effect of nebivolol on stimulation of endothelial NO synthase.[51] These agents, acting mainly through the reduction of peripheral vascular resistance, have little or no effect on cardiac output.[25]

Vasodilatory β-blockers provide additional benefits such as reduced ventricular preload and afterload, improved renal blood flow, enhanced sodium secretion, and favourable effects on myocardial cells.[52] In contrast to traditional β-blockers that do not reduce peripheral vascular resistance, vasodilatory agents might provide beneficial effects on endothelial dysfunction, vascular remodelling, and progression of target organ damage.[52] Atenolol as an example, did not demonstrate improvements in small artery structure and endothelial function despite equal BP-lowering with calcium channel blockers or angiotensin blockers, which did demonstrate improvements.[53] Some of the rationale for lack of atenolol's effect included lack of effect on oxidative stress and peripheral vasoconstriction.[53] Two studies comparing nebivolol and atenolol have shown that nebivolol has a more pronounced effect on reducing aortic pulse pressure and wave reflection and increasing pulse pressure amplification.[54,55] These effects might be due to the associated vasodilation. Because stroke risk is associated with higher central aortic pressure,[56] vasodilatory β-blockers might be more beneficial than atenolol on stroke protection. Whether this will actually translate into additional benefits in terms of morbidity/mortality end points requires further investigation.

In the major clinical trials, β-blockers have been associated with metabolic disturbances.[57] As a class, they have been associated with decreases in insulin sensitivity and an increased incidence of new onset diabetes.[57] Weight gain, attenuation of the β receptor-mediated release of insulin from pancreatic β-cells, and decreased blood flow in skeletal muscle tissue microcirculation are possible mechanisms leading to decreased glucose uptake and increased insulin resistance.[26] These data have come from studies involving traditional selective or nonselective β-blockers, such as atenolol, metoprolol, and propranolol.[58] A meta-analysis of 12 studies reporting data on 94,492 patients has shown a 22% increased risk of new-onset diabetes in patients treated with these 3 agents compared with other classes of antihypertensive agents, with the exception of the diuretic agents.[58]

Recent data emerging from the use of vasodilatory β-blockers suggest that these agents might share neutral or even beneficial effects on metabolic parameters compared with more traditional β-blockers. With regard to lipid abnormalities, agents possessing vasodilatory properties such as carvedilol and nebivolol seem to have a neutral or beneficial effect on lipoprotein lipase activity and levels of triglycerides and high-density lipoprotein cholesterol, in contrast to more conventional older β-blockers.[20] With respect to glycemic effects, results from a study comparing atenolol with nebivolol in patients with impaired glucose tolerance demonstrated that, compared with baseline, atenolol induced a significant reduction in insulin sensitivity and in glucose disappearance rate as measured using a euglycemic hyperinsulinemic clamp and nebivolol showed a neutral effect on these parameters.[59] Similarly, the **G**lycemic **E**ffects in Diabetes **M**ellitus: Carvedilol-Metoprolol Compari**n**s**i**on in Hyperte**n**s**i**ves (GEMINI) study,[60] which compared metoprolol with carvedilol in 1235 patients with diabetes and hypertension, showed that both treatments provided equivalent BP reduction but significantly more patients in the metoprolol group had to discontinue the study because of poor glycemic control. Carvedilol, compared with metoprolol, improved endothelial function and oxidative stress in patients with type 2 diabetes mellitus.[61]

Finally, some have suggested that vasodilatory β-blockers might be better tolerated than nonvasodilatory agents. Studies assessing quality of life suggested that agents such as nebivolol might be as well tolerated as the angiotensin receptor blocker, losartan.[62] Among side effects negatively influencing patient compliance, sexual dysfunction has been reported in up to 20% of patients receiving β-blockers.[17] Nebivolol has been associated with a significant improvement in erectile function compared with traditional β-blockers such as atenolol[63] and metoprolol.[64] It seems that the NO-mediated vasodilatory effects of nebivolol might contribute to sustained erectile function.[63,64]

ISA

The β-blockers, acebutolol, labetalol, and pindolol, exhibit ISA due to partial agonism at 1 or more β-adrenergic receptors. Therefore, this property allows them to permit stimulation of β-adrenoreceptors and blockade of sympathetic nervous system signalling transmission.[42] ISA has been shown to attenuate the decrease in heart rate and cardiac output and the increase in peripheral vascular resistance, respectively produced by the blockade of the β1 and β2 receptors.[65] Consequently, possessing this property might lessen antihypertensive efficacy. Hence, ISA does not seem to provide any advantage in patients with CAD or hypertension because this pharmacologic property has not been associated with any additional benefits in terms of outcomes. In this regard, a metaregression analysis has shown that there was a near significant trend toward a decreased benefit of agents with ISA in patients after an MI.[18,31] However, the **A**cebutolol et **P**révention **S**econdaire de l'**I**nfarctus (APSI) trial has shown that acebutolol still decreases mortality at 5 years in patients who had an MI.[66]

Lipophilicity/hydrophilicity

Lipophilic agents, such as propranolol, metoprolol, and nebivolol[67] have the ability to cross the blood-brain barrier. Lipophilic agents are primarily eliminated by hepatic metabolism and they tend to have shorter half-lives and wider variations in plasma concentrations.[18] Because of their hepatic elimination, they are also generally more prone to clinically significant drug interactions. On the contrary, more hydrophilic agents such as atenolol, sotalol, and nadolol are excreted by the kidneys and therefore need to have their dosage adjusted according to renal function.[68] Sotalol in particular should be used with caution in patients with low glomerular filtration rate (< 20 mL/min) because of the increased risk of torsade de pointes.[69] Because of central nervous system penetration, lipophilic agents are frequently used for the treatment of migraine and essential tremor.[18] With regard to cardiovascular protection, it has been suggested that lipophilic β-blockers might have a different effect on hard end points such as mortality, than hydrophilic agents. Indeed, it has been shown that vagal tone, which has been associated with mortality, might improve after penetration of central nervous system by lipophilic agents.[70] However, a study in 70,000 patients with

MI has not been able to demonstrate that lipophilicity was an important characteristic in preventing mortality.[28]

Lipophilic agents have commonly been identified as molecules with a poor tolerability profile. Some have postulated that the use of these agents might result in a greater incidence of central nervous system effects such as lethargy, confusion, and depression.[68] A meta-analysis reporting results on more than 35,000 patients from 15 different trials has shown that β-blocker use was not associated with a significant risk of depressive symptoms but was associated with a small but significant risk of erectile dysfunction and fatigue.[71] Regarding the risk of fatigue, the authors reported that it was significantly more frequent with early-generation β-blockers (propranolol, timolol) compared with later-developed agents. The degree of lipophilicity was not related to the incidence of side effects.

Who Should Receive β-Blockers in Cardiovascular Medicine?

It remains quite clear that β-blocking agents with their ability to block the β1-adrenergic receptor are the drugs of choice in patients with acute or chronic cardiac ischemia. They are also part of the treatment for patients with heart failure in addition with a renin-angiotensin-aldosterone system inhibition-based treatment. For the treatment of hypertension, the Canadian Hypertension Education Program still recommends their use as a first-line option treatment in patients younger than 60 years of age. However, when addressing the question of the β-blockers place in therapy, the answer lies not in global generalizations but in assessing individual patient needs and specific β-blocking agent characteristics. Poor tolerability often explains the reluctance of some clinicians to recommend β-blockers to their patients. The new third-generation β-blockers with a favourable tolerability profile might represent an alternative in patients presenting side effects and necessitating the use of this cardiovascular class of agents. Further studies are required to demonstrate the efficacy of these agents and their role in the clinician's armamentarium.

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